ENHANCEMENT OF MEMORY BY LITHIUM IN ANIMAL MODEL OF STRESS

Tahira Perveen*, Zehra Batool, Saida Haider and Darakhshan J Haleem
Neurochemistry and Biochemical Neuropharmacology Research Unit,
Department of Biochemistry, University of Karachi, Karachi-75270, Pakistan

Abstract

Numerous studies have consistently shown that repeated restraint stress produces functional neuromorphological and physiological alteration that are linked to the pathophysiology of brain disorder, like depression and bipolar disorder, causes alteration in cognition and learning memory. Lithium is the drug of choice in the treatment of depression and mania in bipolar disorder as a mood-stabilizing agent.

Present study was designed to investigate the effects of long term lithium administration on memory function and its relation with 5-HT metabolism following repeated restraint stress. In this experiment memory was assessed by novel object recognition task in water treated and lithium treated unrestraint and restraint rats. Recognition memory decreased in water treated repeated restraint rats while in lithium treated repeated restraint rats recognition memory increased. 5-HIAA level increased in water treated restraint rats while decreased in lithium treated restraint rats.

The findings indicate a role of brain serotonin in improved memory function in repeated restraint rats following long term lithium administration.

Keywords: Stress, lithium, memory, 5-HIAA.

INTRODUCTION

Human health has been shown to be affected by the stressful events of life in many ways; stress inducing situation alters cognition, learning memory, and emotional responses, causes mental disorders like depression and anxiety (Wood *et al*, 2003; Vasconcellos *et al*, 2003; Post, 1992; Wong & Licinio, 2001). Restraint stress has been proved as an animal model for stress. It is used studying the effects of drugs on stress induced deficits (Kennett, 1986; Pare and Glavin, 1986). Hippocampus is an important brain structure involve in learning and memory (Eichenbaum *et al*, 1992). Repeated restraint stress has been reported to cause an impairment of spatial memory (Luine *et al*, 1994) because of the reason that repeated restraint stress damages brain cells, especially hippocampal neurons (Watanbe *et al* 1992). It has been shown that memory loss in humans has been associated with depression, as the hippocampal volume is reduced (Sheline *et al*., 1996). Chronic restraint stress produces functional, neuromorphological, and physiological alterations that are linked to the pathophysiology of depression and other psychiatric disorders like anxiety and panic disorder (Kleen, *et al*., 2006; Vasconcellos *et al*., 2003). Serotonin is an important neurotransmitter in adaptation to stress (Samad *et al*., 2006) and depression is associated with the hypoactivity of monoaminergic, particularly serotonergic system of the brain (Schloss & Williams 1998; Haleem, 1999). These serotonin containing neurons are shown to be involved in stress-dependent impairments in spatial memory (Luine *et al*., 1994).

Lithium in pharmacology refers to the lithium ion, Li^+, used as a drug in the form of lithium salts like lithium carbonate (Massot *et al*., 1999). Lithium salts have a major impact in the treatment and prophylaxis of mania and bipolar disorder (Dunner & Neumair, 2000) also these salts use as a prophylactic agent in unipolar depression, aggressive behavior and schizophrenic disorder. (Frost & Messiha, 1983). Lithium treatment has been found to attenuate the stress inducing alteration in cognition, learning memory, and emotional responses (Vasconcellos *et al*, 2003).

In view of these neuroprotective effects of lithium in response to stress, present study was designed to investigate the effects of long term lithium administration on memory function and its relation with 5-HT following repeated restraint stress.

MATERIALS AND METHODS

Animal and treatment

Locally bred Albino Wistar rats weighing 180-200gms were used for the experiment. Animals were caged individually in plastic cages with free access to cubes of standard rodent diet and tap water for 3 days before starting the experiment. Body weight and food intake of all rats were monitored in both pre and post experimental period.

Drug Preparation

400mg tablet of Lithium Carbonate was crushed and dissolved in 100ml of deionized water. The drug was given orally at the dose of 1mg/kg/ml for 21 days.

*Corresponding author: E-mail: tahiraatiq@hotmail.com

Experimental Protocol

In the beginning of experiment animals were divided in two groups water and drug treated. Rats were given to standard diet and water throughout the experiment Fresh drug was prepared before starting the experiment. Deionized water was orally administered to water treated rats and Lithium Carbonate (1.0 mg/kg/ml) was orally administered to drug treated animals for 21 days. After 21 days of administration both groups were divided into unrestraint and restraint groups. Restraint groups were stressed for 2 hrs, stress procedure was repeated for 5 days. All the experiments were performed according to the instructions given by animals care committee. Behavioral analysis was performed 24 hrs following repeated restraint stress (2h/day for 5 days). Animals were decapitated after behavioral analysis and brain samples were stored at -70^{o}c for neurochemical analysis.

Restrain Procedure

At the end of 21st day of treatment animals of restrain group (both water and drug treated) were subjected to repeated exposure of 2hrs restraint stress for five days. Restrain was done in separate room to prevent unrestraint animals from being under stressful condition due to disturbance. The animals were restrained by approved procedure as described earlier (Kennett *et al*., 1985, Haleem *et al*., 1988, Haleem and Parveen., 1994). Wire grids of 10" x 9" fitted with a Perspex plate of 9" x 6.5" as described earlier (Haleem *et al*., 1988, Haleem and Parveen, 1994) were used. Immobilization was effected by pressing the fore limbs of the rats through the gaps in the metal grid and tapping them together with zinc-oxide plaster. Hind limbs were also tapped and the head of animal rested on the Perspex plate. Restrain consist of 2hr/day immobilization for 5 days. After 2hr/day restrain stress, rat's legs were released by applying acetone to the tape and return to their home cage.

Behavioral Analysis

Novel Object Recognition Task

The object recognition task is based on the natural tendency of animals to investigate a novel object rather a familiar object when both are simultaneously present in an area. This test was monitored and described by Ennaceur and Delacour (1988). The test was performed in a box having area 45x45 cm with 42 cm high walls constructed of wood. The objects to be discriminated were two transparent glasses (used as novel object). Objects were heavy enough so that rats could not move them. It should be made sure that objects have no natural significance of rats. The two objects should always be placed at the same location within the area during the training and test.

Neurochemical analysis

At the end of the experiment animals were decapitated using guillotine. Brain was removed immediately and stored at -70^{o}C for the determination of 5-HIAA by HPLC-EC as described earlier (Haleem and Haider, 1996).

The effect of lithium on restrained and unrestrained rats on behavioral and neurochemical data were analyzed by two-way ANOVA Post-hoc comparisons were made by using Newman-keuls test.

RESULTS

Fig. 1 shows the effect of long term lithium administration (for 21 days) on recognition memory (sniffing time for new object in sec.) in unrestraint and repeated restraint rats.

Data analyzed by two-way ANOVA (df=1,20) show non significant effect of repeated restraint stress ($F=2.00$, $p > 0.05$), significant effect of drug ($F=6.66$, $p<0.05$) and non significant interaction between two factors ($F=0.56$, $p>0.05$).

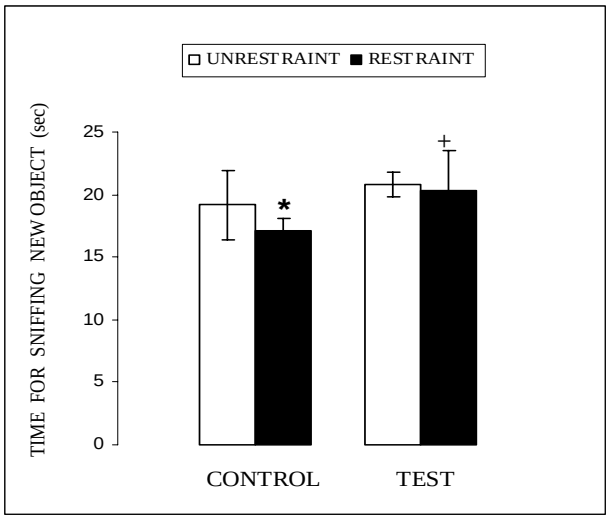

Fig. 1. Values are mean ±S.D (n=6). Significant differences by Newman-keuls test:*P<0.05 from their respective unrestraint controls; ±P<0.05 from respective water treated controls.

Post-hoc analysis by Newman-keuls test showed that recognition memory significantly decrease ($p<0.05$) in restraint control animals whereas, long term lithium administration significantly increase ($p<0.05$) recognition memory in restraint rats.

Fig. 2 shows the effect of long term lithium administration on brain 5-HIAA level in unrestraint and repeated restraint rats.

Data analyzed by two-way ANOVA (df=1,20) show non significant effect of repeated restraint stress ($F=.073$, $p>0.05$), non significant effect of drug ($F=1.34$, $p>0.05$)

and significant interaction between two factors (F=14.47, p<0.01).

Post-hoc analysis by Newman-keuls test showed that 5-HIAA level significantly increased (p<0.05) in restraint control animals, and it is also observed that 5-HIAA level significantly decreased (p<0.05) and increased (p<0.05) in lithium treated restraint and restraint rats respectively. Long term lithium administration significantly decreased (p<0.05) 5-HIAA level in repeated restraint rats.

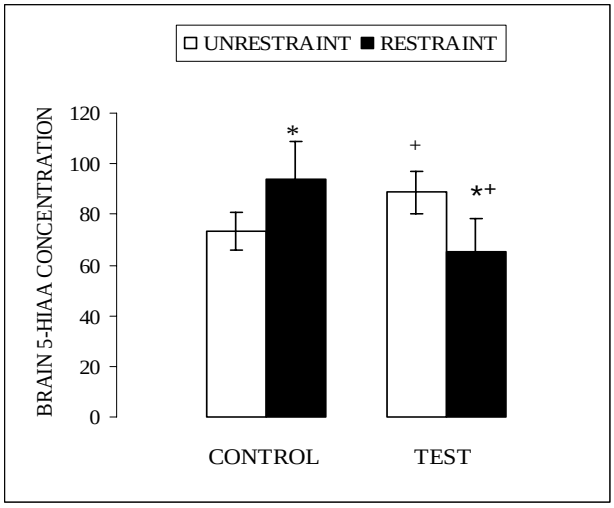

Fig. 2. Values are mean +S.D (n=6). Significant differences by Newman-keuls test:*P<0.05 from their respective unrestraint controls; ± P<0.05 from respective water treated controls.

DISCUSSION

Lithium used as a drug in the form of lithium salts like lithium carbonate (Massot *et al*., 1999). In bipolar depression, lithium salts use as a mood stabilizing drugs and have a role in the treatment of depression and more particularly of mania. (Bowden, 1978; Noyes *et al*., 1974).

Cognition is the process of knowing and, more precisely, the process of being aware, thinking, learning, and judging. In present study, cognition is analyzed by novel object recognition task and we found that repeated restraint stress significantly decreased recognition memory i.e. impairment of cognitive function occurred. Previously it is reported that repeated restraint stress caused cognitive impairment. (McEwen *et al*., 1997). It is reported that immobilization stress impaired the long term potentiation induction in hippocampus whereas lithium showed protective effect against stress-induced impairment of long term potentiation induction (Lim *et al*, 2005).

In the present study it is found that recognition memory significantly improves by lithium treatment in repeated restraint stress these results are strongly supported by the previous findings (Yazlovitskaya *et al*., 2006). 5-HT involve in a variety of neuronal function such as pain, feeling, sleep, cardiac regulation, it has also important role in cognition (McEntee & Crook, 1991; Zakzanis and Young, 2001). Increased 5-HIAA levels following repeated restraint stress observed in the present study may be due to increased 5-HT turnover that may be possibly involve in memory impairment. These increase in 5-HIAA levels were not observed in lithium treated repeatedly restraint rats. However, 5-HIAA levels significantly decreased in these rats. Enhancement of memory function with decreased 5-HIAA levels in lithium treated restraint rats suggest that decreased 5-HT turnover is a possible mechanism for the memory enhancement.

CONCLUSION

In conclusion it is suggested that enhanced memory function with decreased 5-HIAA levels following Li administration in restraint rats may be due to decreased brain serotonin turnover. These results emphasize the neuroprotective role of lithium treatment.

REFERENCES

Bowden CL. (1978). Lithium-responsive depression; Compr Psychiatry. 19(3):227-31.

Dunner DL and Neumaier JF. (2000). Chapter 24 lithium use in clinical practice. Principles of Medical Biology. 14:569-583.

Eichenbaum H, Otto T and Cohen NJ. (1992). The hippocampus: What does it do? Behav. Neural Biol. 57:2-36.

Ennaceur A and Delacour J. (1988). A new one trail test for neurobiological studies of memory in rats. Behavioral Brain Research. 31:47-59.

Frost RE and Messiha FS. (1983). Clinical uses of lithium salts. Brain Res Bull. 11(2):219-31.

Haleem DJ and Haider S. (1996). Food restriction decreases serotonin and its synthesis rate in hypothalamus. Neuro Report. 7: 1153-1156.

Haleem DJ, Kennett GA and Curzon G. (1988). Adaptation of female rats to stress shift to male pattern by inhibition of corticosteron. Brain Res. 45:339-347.

Haleem DJ and Parveen T. (1994). Brain regional serotonin synthesis following adaptation to repeated restraint. Neuroreport.5(14):1785-1788.

Haleem DJ. (1999). Attenuation of 8-OH-DPAT-inducted decreases in 5-HT synthesis in brain regions of rat adapted to a repeated stress schedule. Neuroscience. 3(2):123-129.

Kennett GA, Dickinson SI and Curzon G. (1985). Enhancement of some 5-HT dependent behavioral responses following repeat immobilization in rats. Brain Res. 330:253-263.

Kennett G. A, Chaouloff F, Marcou M and Curzon G. (1986). Female rats are more vulnerable than males in an animal model of depression: the possible role of serotonin. Brain Res. 382:416-421.

Kleen JK, Sitomer MT, Killeen PR and Conrad CD. (2006). Behav Neurosci. 120(4):842-851.

Lim KY, Yang JJ, Lee Deok S, Noh Jai Sung, Jung Min W and Chung Young-Ki. (2005). Lithium attenuates stress-induced impairment of long-term potentiation induction [neurophysiology, basic and clinical]. NeuroReport. 16(14): 1605-1608.

Luine V, Villegas M and Martinez C (1994). Stress-dependent impairments of spatial memory; role of 5-HT. Ann NY Acad Sci. 746:403-404.

Massot O, Rousselle JC, Fillion MP, Januel D, Plantefol M and Fillion G. (1999). 5-HT1B receptors: a novel target for lithium. Possible involvement in mood disorders. Neuropsychopharmacology. 21(4):530-41.

McEntee WJ and Crook TH. (1991). Serotonin, memory, and the aging brain. Journal Psychopharmacology. 103(2):143-149.

McEwen BS, Conrad CD, Kuroda Y, Frankfurt M, Magarinos AM and McKittrick C. (1997). Prevention of stress-induced morphological and cognitive consequences. Eur Neuropsychopharmacol. 7(Suppl 3):S323-8.

Noyes R, Dempsey GM, Blum A and Cavanaugh GL. (1974). Lithium treatment of depression. Compr Psychiatry. 15(3):187-93.

Paré W P and Glavin GB. (1986). Restraint stress in biomedical research: A review. Neuroscience & Biobehavioral Reviews. 10(3):339-370.

Post, RM. (1992). Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. American Journal of Psychiatry.149:999-1010.

Samad N, Parveen T, Haider S and Haleem DJ. (2006). Attenuation of stress induced behavioral deficits by Azadirachta indica (neem): Role of serotonin. Pak. J. Bot. 38(1):131-138.

Schloss P and Williams DC. (1998). The Serotonin transporter: A primary target for antidepressant drugs. J Psychopharmacol. 12(2):115-21.

Sheline YI, Wang PW, Gado MH, Csernansky JG and Vannier MW. (1996). Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci USA. 93:3908-3913.

Vasconcellos APS, Tabajara AS Ferrari C, Rocha E and Dalmaz C. (2003). Effect of chronic stress on spatial memory in rats is attenuated by lithium treatment. Physiology and Behavior. 79(2):143-149.

Watanabe Y, Goulde E and McEwen BS. (1992). Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. Brain Res. 588:341-345.

Wong ML and J Licinio. (2001). Research and treatment approaches to depression. Nature Reviews Neuroscience. 2:343-351.

Wood GE, Young LT, Reagan LP and McEwen BS. (2003). Acute and chronic restraint stress alter the incidence of social conflict in male rats. Horm Behav. 43(1):205-13.

Yazlovitskaya EM, Edwards E, Thotala D, Fu A, Osusky KL1, Whetsell WO, Boone B, Shinohara ET and Hallahan DE. (2006). Lithium treatment prevents neurocognitive deficit resulting from cranial irradiation. Cancer Research. 66:11179-11186.

Zakzanis KK and Young DA. (2001). Memory impairment in abstinent MDMA (Ecstasy) users: A longitudinal investigation. Neurology. 56:966-969.

Received: 25-05-2011
Accepted: 07-06-2011